App. No.: 10/801,443
Art Unit: 1624

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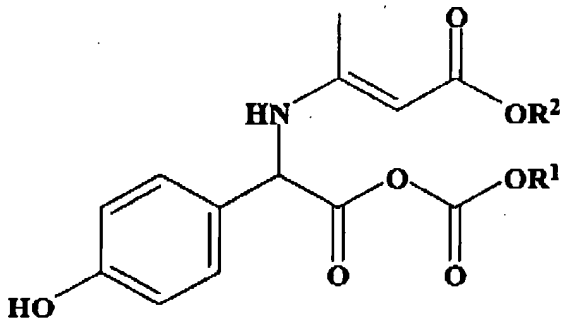
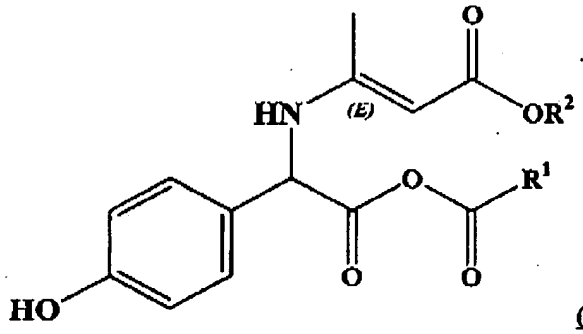
Amendments to the Specification

Please amend the paragraph beginning at page 4, line 15 and ending at page 5, line 7 with the following amended paragraph:

Of the activated derivatives of 4-hydroxyphenylglycine, the mixed anhydride of α-amino-p-hydroxyphenylacetic acid of formula III or IIIa:



(III)



(IIIa)

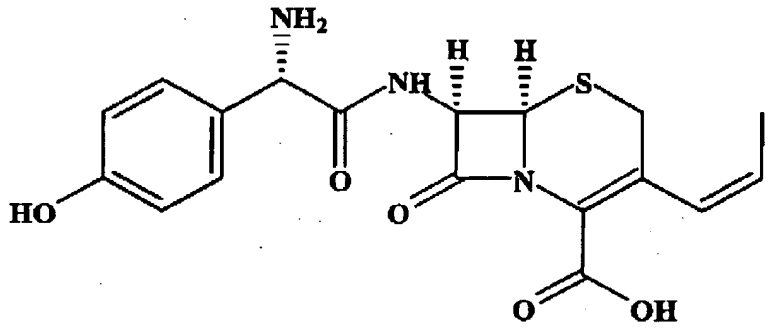
wherein R1 is an alkyl or an aryl group and R2 is methyl or ethyl,

is generally prepared by reacting N-substituted-α-amino-p-hydroxyphenylacetic acid or its salt (Dane salt) with an appropriate acylating agent at an appropriate temperature. For example in the process disclosed in US 3,985,741, the mixed anhydride is prepared by adding the acylating agent, base and the Dane salt to dry acetone at –10°C and stirring the slurry for 20 minutes. As per the process disclosed in US 4,218,474, the mixed anhydride is prepared by adding a

chloroformate, such as ethylchloroformate, to a solution of N-protected-4-hydroxy phenylglycine dissolved in an inert organic solvent at a temperature of –5° to 0°C in the presence of a base. According to the method disclosed in WO03/011871, the mixed acid anhydride is prepared by adding a base and Dane salt to an inert organic solvent at ambient temperature, cooling the suspension to –30°C, followed by addition of the acylating agent and stirring.

Please amend the paragraph beginning at page 8, line 20 and ending at page 10, line 4 with the following amended paragraph:

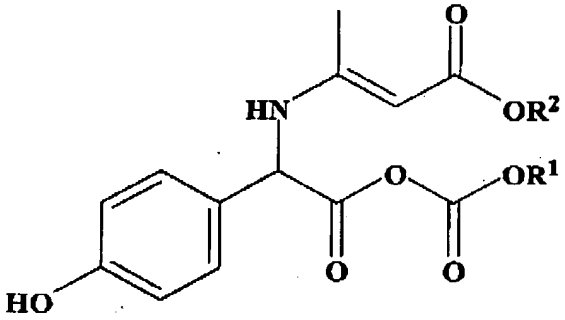
Thus the main aspect of the present invention relates to process for preparation of Cefprozil of formula (I)



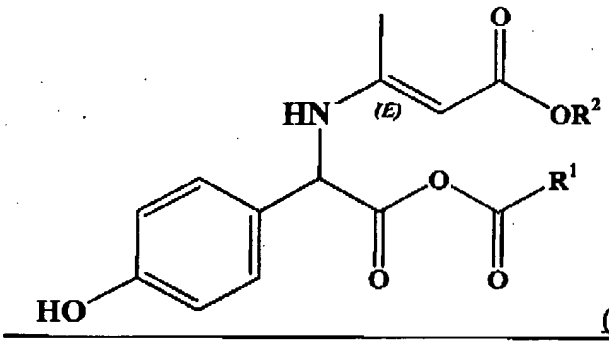
(I)

in the form of a monohydrate comprising of

reacting the mixed anhydride of α-amino-p-hydroxyphenylacetic acid of formula (III) or (IIIa)



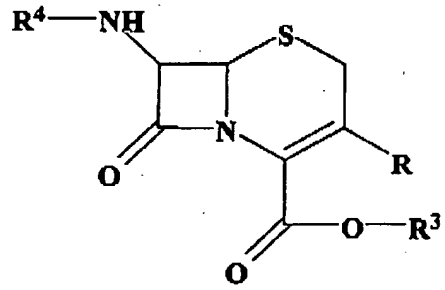
(III)



(IIIa)

wherein R^1 is an alkyl or an aryl group and R^2 is methyl or ethyl,

with a protected 7-amino-3-(propen-1-yl)-3-cephem-4-carboxylic acid of formula (VII)



(VII)

wherein R^3 and R^4 are protective groups, R is propen-1-yl,

followed by hydrolysis, isolation and purification to give Cefprozil of formula (I) in the form of a monohydrate in high yield and purity, substantially free of impurities.

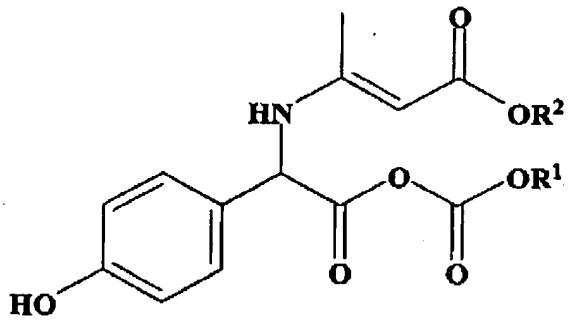
Please replace the paragraph beginning at page 10, line 16 and ending at page 10, line 18 with the following amended paragraph:

The effect of varying sequence addition of reagents during mixed anhydride preparation on the amount of total impurities formed along with Cefprozil was established by the following experimental evidence.

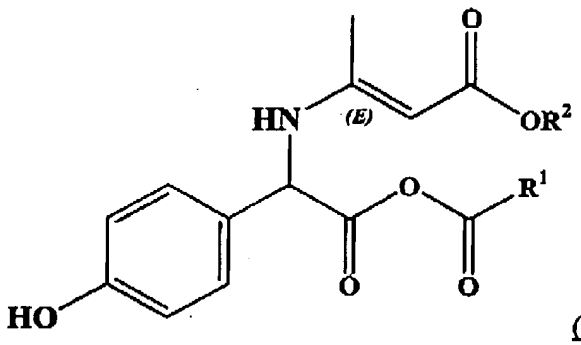
Please replace the paragraph beginning at page 17, line 15 and ending at page 18, line 15 with the following amended paragraph:

According to a preferred aspect of the invention, there is provided a process for preparation of Cefprozil in the form of a monohydrate, comprising steps of:

reacting a mixed acid anhydride of α-amino-p-hydroxy phenylacetic acid of formula (III) or (IIIa)



(III)



(IIIa)

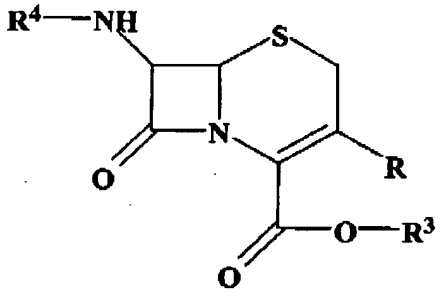
wherein R^1 is an alkyl or an aryl group and R^2 is methyl or ethyl, the mixed acid anhydride prepared by a process comprising the steps of

(a) adding an acylating agent and a base to a mixture of an inert organic solvent and a polar aprotic solvent at a temperature in the range of 0° to 40°C, preferably 20° to 25°C;

(b) cooling the solution to a temperature in the range of –70° to –30°C, preferably –35°C to –50°C;

(c) addition of Dane salt of an α-amino-p-hydroxy phenylacetic acid to the cooled solution and agitation at a temperature in the range of –70° to –30°C, preferably –35°C to –50°C.

with a protected 7-amino-3-(propen-1-yl)-3-cephem-4-carboxylic acid (7-APCA) of formula (VII)



(VII)

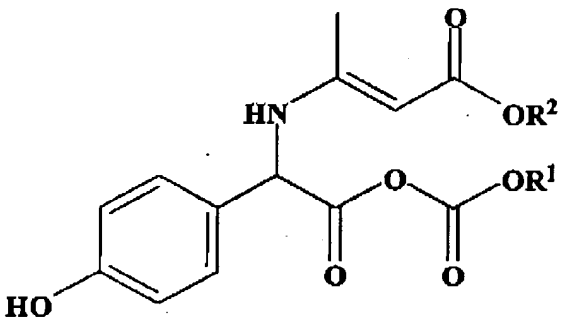
wherein R^3 and R^4 are protective groups, R is propen-1-yl,

followed by hydrolysis, isolation and purification to give Cefprozil of formula (I) in the form of a monohydrate in high yield and purity, substantially free of impurities.

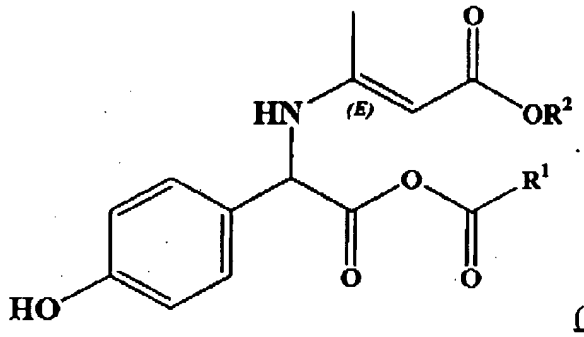
Please replace the paragraph beginning at page 18, line 16 and ending at page 20, line 4 with the following amended paragraph:

According to a preferred aspect of the invention, there is provided a process for preparation of Cefprozil in the form of a monohydrate, comprising steps of:

reacting a mixed acid anhydride of α-amino-p-hydroxy phenylacetic acid of formula (III) or (IIIa)



(III)



(IIIa)

wherein R^1 is an alkyl or an aryl group and R^2 is methyl or ethyl, the mixed acid anhydride prepared by a process comprising the steps of

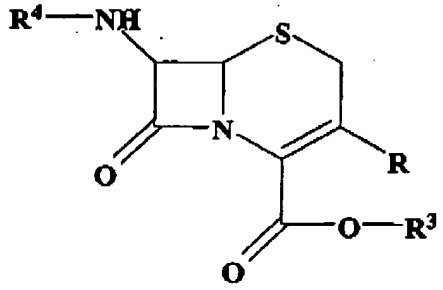
(a) adding an acylating agent and a base to an inert organic solvent at a temperature in the range of 0° to 40°C, preferably 20° to 25°C;

(b) cooling the solution to a temperature in the range of –70° to –30°C, preferably –35°C to –50°C;

(c) addition of Dane salt of an α-amino-p-hydroxy phenylacetic acid to the cooled solution and agitation at a temperature in the range of –70° to –30°C, preferably –35°C to –50°C.

(d) addition of a polar aprotic solvent to the above solution and agitation at a temperature in the range of –70° to –30°C, preferably –35°C to –50°C.

with a protected 7-amino-3-(propen-1-yl)-3-cephem-4-carboxylic acid (7-APCA) of formula (VII)



(VII)

wherein R^3 and R^4 are protective groups, R is propen-1-yl,
followed by hydrolysis, isolation and purification to give Cefprozil of formula (I) in the form of a monohydrate in high yield and purity, substantially free of impurities.

Please replace the paragraph beginning at page 25, line 25 and ending at page 26, line 7 with the following amended paragraph:

To a mixture of methylene chloride (125 ml) and N,N-dimethylformamide (85 ml), cooled to 20°C-25°C, is added a solution of N-methylmorpholine in dichloromethane (0.25 g, 0.0025 mole in 5 ml) and ethyl chloroformate in dichloromethane (12.72 g, 0.117 mole in 10 ml) under stirring. The resulting solution is cooled to –40°C to –50°C and potassium D-N-(2-methoxycarbonyl-1-methylvinyl)-α-amino-α-(4-hydroxylphenyl) acetate (33.14 g, 0.11 mol) is

added to it. The suspension is agitated at –40°C to –35°C for 120 minutes. The reaction mass which is a solution of mixed anhydride product is cooled to –70 °C for condensation.

Please replace the paragraph beginning at page 26 line 16 and ending at page 26 line 27 with the following amended paragraph:

To a solution of the mixed anhydride product of procedure ~~1b~~ 1A, cooled to –70 °C, is added with stirring, a cooled solution of the disilylated 7-APCA as prepared by procedure 1a. The reaction mixture is stirred at –50° to –40°C and monitored by HPLC till quantitative conversion to the silylated Cefprozil is achieved. The reaction time is about 4 hours. The resulting reaction mass is added to a mixture of 85 ml water and 20 ml concentrated hydrochloric acid maintained at –40°C to –20°C. The temperature of the reaction mass is raised to 5°C to10°C and the pH of the solution is adjusted to 0.5 with concentrated hydrochloric acid. The reaction mass is stirred for 30 minutes and the layers are separated. The aqueous layer is diluted with acetone (75 ml) followed by the addition of 2.5 g of activated carbon and sodium dithionite (0.25 g) to remove the colored solid impurities. The reaction temperature is maintained at 10° to15°C.

Please replace the paragraph beginning at page 27, line 8 and ending at page 27, line 16 with the following amended paragraph:

Methylene chloride (125 ml) is cooled to 20°C – 25°C, and a solution of N-methylmorpholine in dichloromethane (0.25 g, 0.0025 mole in 5 ml) and ethyl chloroformate in dichloromethane (12.72 g, 0.117 mole in 10 ml) under stirring. The resulting solution is cooled to –40°C to –50°C and potassium D-N-(2-methoxycarbonyl-1-methylvinyl)-α-amino-α-(4-hydroxylphenyl) acetate (33.14 g, 0.11 mol) is added to it. The suspension is agitated at –40°C to –35°C for 120 minutes. The reaction mass which is a solution of mixed anhydride product is cooled to –70°C for condensation.

Please replace the paragraph beginning at page 27, line 25 and ending at page 28, line 9 with the following amended paragraph:

To a solution of the mixed anhydride product of procedure [[1b]]2A, cooled to –70 °C, is added with stirring, a cooled solution of the disilylated 7-APCA as prepared by procedure 1a. The reaction mixture is stirred at –50° to –40°C and monitored by HPLC till quantitative conversion to the silylated Cefprozil is achieved. The reaction time is about 4 hours. The resulting reaction mass is added to a mixture of 85 ml water and 20 ml concentrated hydrochloric acid maintained at –40°C to –20°C. The temperature of the reaction mass is raised to 5°C to10°C and the pH of the solution is adjusted to 0.5 with concentrated hydrochloric acid. The reaction mass is stirred for 30 minutes and the layers are separated. The aqueous layer is diluted with acetone (75 ml) followed by the addition of 2.5 g of activated carbon and sodium dithionite (0.25 g) to remove the colored solid impurities. The reaction temperature is maintained at 10° to15°C.